2002/110 PCT

5

**PCT** WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)


(51) International Patent Classification 6 :
A61L 15/18, 15/44, A61K 9/70, 9/00, A61N 1/30

A1

(11) International Publication Number: **WO 98/58685**

(43) International Publication Date: 30 December 1998 (30.12.98)

(21) International Application Number: PCT/EP98/03796

(22) International Filing Date: 22 June 1998 (22.06.98)

(30) Priority Data:
MI97A001475 23 June 1997 (23.06.97) IT



(71) Applicant *(for all designated States except US)*: LABORATORIO ITALIANO BIOCHIMICO FARMACEUTICO LISAPHARMA S.P.A. [IT/IT]; Via Licinio, 11, I–22036 Erba (IT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BOCCHIALINI, Bianca, Maria [IT/IT]; Via Langhirano, 119, I–43100 Parma (IT). CATELLANI, Pier, Luigi [IT/IT]; Via Bologna, 24, I–42100 Reggio Emilia (IT). COLOMBO, Paolo [IT/IT]; Via Inzani, 1, I–43100 Parma (IT). SANTI, Patrizia [IT/IT]; Via Micheli, 5, I–43039 Salsomaggiore (IT). ZAGNOLI, Giorgio [IT/IT]; Via Rubini, 10, I–22100 Como (IT).

(74) Agent: GERVASI, Gemma; Notarbartolo & Gervasi, Corso di Porta Vittoria, 9, I–20122 Milano (IT).



(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

**Published**
*With international search report.*
*Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.*


(54) Title: DERMAL ADHESIVE PLASTER SUITABLE FOR TREATING LOCALIZED CUTANEOUS AFFECTIONS


(57) Abstract

Dermal adhesive plaster having high mechanical strength, flexibility, transparency and electric conductivity, comprising: a) a backing layer containing: a polymer insoluble in water, a thickening agent, and a humectant; b) an adhesive layer that may possibly act as a depot for the active principle, containing: an adhesive polymer and a humectant, characterized in that both the backing layer and the adhesive layer contain an electrolyte. The plaster may be used in the treatment of localized cutaneous affections that require a prompt availability of the active principle, with permanence of the same in the site of action. The said cutaneous affections may include local inflammation and infected cutaneous ulcerations.

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| AL | Albania | ES | Spain | LS | Lesotho | SI | Slovenia |
| AM | Armenia | FI | Finland | LT | Lithuania | SK | Slovakia |
| AT | Austria | FR | France | LU | Luxembourg | SN | Senegal |
| AU | Australia | GA | Gabon | LV | Latvia | SZ | Swaziland |
| AZ | Azerbaijan | GB | United Kingdom | MC | Monaco | TD | Chad |
| BA | Bosnia and Herzegovina | GE | Georgia | MD | Republic of Moldova | TG | Togo |
| BB | Barbados | GH | Ghana | MG | Madagascar | TJ | Tajikistan |
| BE | Belgium | GN | Guinea | MK | The former Yugoslav Republic of Macedonia | TM | Turkmenistan |
| BF | Burkina Faso | GR | Greece | | | TR | Turkey |
| BG | Bulgaria | HU | Hungary | ML | Mali | TT | Trinidad and Tobago |
| BJ | Benin | IE | Ireland | MN | Mongolia | UA | Ukraine |
| BR | Brazil | IL | Israel | MR | Mauritania | UG | Uganda |
| BY | Belarus | IS | Iceland | MW | Malawi | US | United States of America |
| CA | Canada | IT | Italy | MX | Mexico | UZ | Uzbekistan |
| CF | Central African Republic | JP | Japan | NE | Niger | VN | Viet Nam |
| CG | Congo | KE | Kenya | NL | Netherlands | YU | Yugoslavia |
| CH | Switzerland | KG | Kyrgyzstan | NO | Norway | ZW | Zimbabwe |
| CI | Côte d'Ivoire | KP | Democratic People's Republic of Korea | NZ | New Zealand | | |
| CM | Cameroon | | | PL | Poland | | |
| CN | China | KR | Republic of Korea | PT | Portugal | | |
| CU | Cuba | KZ | Kazakstan | RO | Romania | | |
| CZ | Czech Republic | LC | Saint Lucia | RU | Russian Federation | | |
| DE | Germany | LI | Liechtenstein | SD | Sudan | | |
| DK | Denmark | LK | Sri Lanka | SE | Sweden | | |
| EE | Estonia | LR | Liberia | SG | Singapore | | |

# DERMAL ADHESIVE PLASTER SUITEBLE FOR TREATING LOCALIZED CUTANEOUS AFFECTIONS

## FIELD OF THE INVENTION

The present invention regards a dermal adhesive plaster having high mechanical strength, flexibility, transparency and electric conductivity, for releasing, in the area of application on the skin delimited by its surface, quantities of medicament capable of having locally a pharmacological effect in the treatment of localized cutaneous affections.

The characteristics of mechanical strength, flexibility, transparency and electric conductivity are essential for promoting transport of the medicament into the skin following a mechanical action, such as massaging or via the use of electrical or radiant energy.

## STATE OF THE ART

The most common skin affections are those caused by bacterial infections or by the local release of irritating substances, such as histamine. In fact, lesions regarding the surface of the skin may often be subject to bacterial contamination of various nature, whilst the release of histamine is linked to the presence of a cellular injury of any cause, which may range from mechanical pressure exerted by a foreign body on a given area of the body to a mere insect sting.

The histamine released in the skin as a result of an insect sting induces a characteristic triad of phenomena known as Lewis' reaction or triple response. This response comprises the rapid formation of a patch of reddening which extends for a few millimetres around the site of the lesion due to the vasodilator effect exerted directly by the histamine on small blood vessels. Subsequently there is the formation of an area of brighter flush or flare (erythema), with irregular boundaries, which extends beyond the initial red patch and is due to axon reflexes induced by the histamine, which are also able to cause vasodilatation. Finally, there is the formation of a weal, which occupies the same area as the initial red patch and is due to the increase in permeability of the capillaries, with consequent formation of oedema. To complete this skin lesion there is added the troublesome capacity of histamine to stimulate various nerve endings, giving rise to an itching

sensation. It moreover frequently happens that the lesions caused by insect stings become acute owing to the particular sensitivity of the patient or to scratching of the skin, with the risk of producing bacterial infections.

In the conditions where the alteration of the skin is characterized by the presence of a solution of continuity in the integrity of the skin, caused by the presence of a lesion or by the "sting" of the insect, it could prove useful to obtain high concentrations of antihistaminic or anti-inflammatory medicament in the affected area, by possibly exploiting, for transport of the medicament, the presence of the lesion itself or of the puncture left by the sting.

There exist on the market dermatological creams that may be spread on the wound to combat the onset of a bacterial infection or to counteract symptoms linked to the local release of histamine. These are semisolid oil in water emulsions, which for their application involve being spread so as to allow the loss of the aqueous component (approximately 80%) and the formation of a very thin film (10-30 μm) in which are present the non-volatile components of the formulation and the medicament.

However, although the medicament is concentrated in the proximity of the area of application of the cream, the quantity of medicament available for absorption is indeterminate and not very reproducible, in particular on account of the poor control of the dose deposited on the skin and of the surface over which this dose is spread out.

Consequently, the lack of reproducibility due both to the non-dosed amount of medicament applied and to the brief period of application render the absorption of the active principle from a dermatological cream so low as to make the application thereof at times ineffective. It should also be added that it may not always be pleasant for the person affected by a skin reaction to apply a cream that leaves visible residues in the area of application.

In the last few years, the use of adhesive plasters that may be applied on the skin for topical administration of medicaments has been revalued. These plasters are more precisely named dermal systems and find use in the direct and localized treatment of cutaneous affections. For this activity a more or less high accumulation of the active principle is in fact required in a limited area of the

epidermis, with the attempt to limit as much as possible the passage of the active principle into the systemic circulation.

The Japanese patent application JP60069016 describes a plaster in which the adhesive layer contains dexamethasone esterified in position 21 together with diphenhydramine for the treatment of insect stings. The adhesive polymer is an ester of (meth)acrylic acid. This plaster presents the drawback that the type of solvent used for the preparation of the adhesive layer is ethyl acetate. The application of a plaster containing such a solvent creates by no means indifferent problems of irritation in the area of the skin which is already inflamed owing to the presence of the insect sting.

The international patent application WO 93110163 describes a hydrogel material comprising an aqueous mixture containing at least one water-soluble adhesive polymer that is able to crosslink, a humectant in a concentration such as to partially inhibit this reticulation, and a reticulation promoter in concentrations such as to inhibit the inhibitory effect of the moistening substance.

This gel, which may possibly contain bactericidal additives, and pharmacological and antibiotic agents, may contain either an electrolyte or, alternatively a therapeutic agent, among which also an antihistaminic agent.

When it contains the electrolyte, this material is used in combination with a substrate that is able to conduct electricity in the preparation of electrically conductive cicatrizing bandages.

When this material contains the active principle, among which also the antihistamine, it does not contain, however, the electrolyte.

The international patent application WO 9310201 describes a hydrogel material similar to the previous one, which alternatively may contain an electrolyte, or else a therapeutic active principle.

When this hydrogel contains the electrolyte, it is used for the preparation of electrically conductive bandages, whereas when it contains the active principle alone, it is used as an adhesive layer for transdermal plasters or apparatuses for iontophoresis.

**SUMMARY OF INVENTION**

The subject of the present invention is a dermal plaster having high mechanical

strength, flexibility, transparency and electric conductivity, comprising:

a) a backing layer containing:

- a polymer insoluble in water,
- a thickening agent,
- a humectant;

b) an adhesive layer possibly containing the active principle and:

- an adhesive polymer,
- a humectant,

characterized in that both the backing layer and the adhesive layer contain an electrolyte.

The plaster may in particular be used in the treatment of localized cutaneous affections that require a prompt availability of the active principle, with permanence of the same in the site of action.

The characteristics of mechanical strength, flexibility, transparency and electric conductivity are essential for promoting transport of the medicament into the skin following on massaging or via the use of electrical or radiant energy.

The application of the dermal plaster which is the subject of the present invention represents a solution to the problem of topical administration of medicament in so far as it offers the following advantages:

1. a therapeutic intervention characterized by ease of application of the adhesive plaster on the wound;

2. creation of a high gradient of concentration of the medicament in the area of the wound and persistence of this gradient for the whole time of application of the plaster;

3. partial occlusion of the area involved in transporting the medicament;

4. protection of the lesion from friction resulting from impact against clothes or foreign bodies or from scratching of the skin as a consequence of pruritus as in the case of insect stings;

5. possibility of accelerating the transport of medicament with the application of laser rays or electric current.

The high gradient of concentration that is set up at the site of the lesion, due to a precise dose of medicament deposited in contact with the site involved in the

therapeutic treatment, and its maintenance over a long period of time increase both the rate of absorption and the amount of active principle absorbed by the skin (bio-availability). In addition, the partial occlusion of the affected area, by favouring hydration of the keratinous layer, constitutes a further factor capable of increasing absorption of the medicament.

Of particular utility is the action of protection that the plaster may perform in regard to a lesion, an action which becomes of importance in the case of an insect sting. In this case, the accidental contact with clothing or foreign bodies provokes itching, which frequently leads the subject to scratch his skin, with the consequent risk of worsening the inflammation, possibly adding complications of infection.

Finally, passage of the medicament through the skin, which under normal conditions takes place by passive transportation after a more or less prolonged period of latency, may be increased by means of an action of massaging carried out directly on the affected area but with the interposition of the plaster. Such massaging produces relief in the case of itching, at the same time favouring a greater penetration of the medicament in conditions of protection for the lesion itself. In addition, the application of energy sources, such as laser beams or electric potential on the plaster applied on the lesion enables the action of promotion of permeation to increase. For this reason, the plaster possesses characteristics of electric conductivity (electric current) and transparency (laser beams).

**DESCRIPTION OF FIGURES**

Figure 1 shows the pattern of pruritus as a function of time after application of the plaster containing 4 mg (—▲—), 10 mg (—●—) of promethazine hydrochloride and placebo (—□—).

Figure 2 gives the area of the weals as a function of time after application of the plaster containing 4 mg (■) 10 mg (□) of promethazine hydrochloride and placebo (■) following to massaging of the skin.

Figure 3 shows the pattern of pruritus as a function of time after application of the plaster containing 4 mg (—▲—), 10 mg (—●—) of promethazine hydrochloride, and placebo (—□—) following on 1 minute of ionophoresis (density of current: 0.25 mA/cm$^2$).

## DETAILED DESCRIPTION OF INVENTION

The electrolyte used both in the adhesive layer and in the backing layer is preferably a halide of an alkaline or alkaline-earth metal; according to a particularly preferred embodiment, this halide is chosen from among sodium chloride, potassium chloride, and magnesium chloride.

The water-insoluble polymer that is present in the backing layer is preferably chosen from polyethylene, polypropylene, polyurethane, polyacrylate, polyethylene terephthalate, polypropylene terephthalate, and polymethacrylate.

The thickening agent used in the backing layer is preferably chosen from between xanthan gum and cellulose and derivatives thereof. The humectant namely the substance that is able to maintain a certain degree of humidity, which is contained both in the backing layer and in the adhesive layer of the dermal plaster that is the subject of the present invention is preferably chosen from among glycerine, sorbitol, propylene glycol, and polyethylene glycol.

Preferably the composition used for the preparation of the backing layer contains between 50 wt% and 99 wt%, more preferably between 80 wt% and 99 wt%, of a suspension or aqueous dispersion containing the water-insoluble polymer.

According to a particularly preferred embodiment, this aqueous suspension contains 40% of esters of polymethacrylic acid and is available on the market under the trade name Eudragit® NE 40 D.

The composition used to prepare the backing layer preferably contains the electrolyte in a concentration of between 0.001 % and 5 %, by weight calculated on the total weight of the said composition.

According to a particularly preferred embodiment, the electrolyte is NaCl.

The thickening agent is preferably present in a concentration of between 0.005% and 5%; according to a particularly preferred embodiment, the said thickening agent is hydroxypropyl cellulose.

The humectant, nemely the substance that is able to maintain a certain degree of humidity is preferably contained both in the backing layer and in the adhesive layer in concentrations of between 0.01% and 5%. According to a particularly preferred embodiment, this substance is glycerine.

The backing layer is obtained by spreading evenly a certain amount of the above-

mentioned composition on a thermo-resistant glass plate and drying the layer obtained in an air-circulation oven for 3 hours at a temperature of 40°C. After drying, a flexible, transparent, gas-permeable and electrically conductive backing is obtained having a thickness of between 0.01 mm and 0.8 mm.

The second layer, which performs the role of depot for the medicament and at the same time that of an adhesive, may be obtained by using a polymer chosen from among polyaminomethacrylate, polyisobutylene, silicone, polyvinyl alcohol, arabic gum, rosin, and abietic acid.

According to a particularly preferred embodiment, the composition used for the adhesive layer comprises between 5 wt% and 90 wt% of an aqueous dispersion containing in turn one of the above-mentioned adhesive polymers. According to a more particularly preferred embodiment, this aqueous dispersion contains between 20 wt% and 40 wt% of polyaminomethacrylate.

Such aqueous dispersions are available on the market under the trade mark PLASTOID® E35.

The concentration of the electrolyte in the adhesive composition ranges from0.001 and 5% by weight calculated on the total weight of said composition.

The humectant, namely the substance capable of maintaining a certain degree of humidity is preferably contained in the adhesive composition in concentration of between 0.01 wt% and 5 wt%, and according to a particularly preferred embodiment this substance is sorbitol.

Also in this case a given quantity of the above-mentioned composition used for preparing the adhesive layer is spread out on the film making up the backing layer.

The ensemble of backing layer and adhesive layer thus obtained is put in an air-circulation oven for 1 hour at a temperature of 90°C. After being cooled to room temperature, it is removed from the glass plate and adhered to a protective liner; in this way, a sheet consisting of a protective liner, adhesive layer and backing layer is obtained, from which round plasters are cut having an area of between 0.1 $cm^2$ and 500 $cm^2$.

This plaster, which has thickness of between 0.03 mm and 1 mm (liner excluded) has proved to be strong, flexible, transparent and electrically conductive, where

the characteristics of transparency and conductivity are indispensable for the use of physical promoters of absorption, such as laser beams and electric current. The dermal plaster which is the subject of the present invention is in fact even more effective in reducing the formation of the weal and in counteracting the sensation of itching when, after it has been applied on the insect sting, a slight massaging is performed on it, or else when a direct current is applied having a density preferably of between 0.01 and 0.8 $mA/cm^2$.

The applicant has moreover unexpectedly found that the dermal plaster which is the subject of the present invention, even in the absence of active principle, is able to reduce the sensation of pruritus when an electric current is applied on it having a density preferably of between 0.01 and 0.8 $mA/cm^2$.

Hence, a further object of the present invention is the transdermal plaster, which does not contain the active principle, as well as its use in reducing the sensation of pruritus in the case where electric current is applied to it.

In addition, the fact that the composition for the adhesive layer is water-soluble renders elimination of any residue left by the plaster easier, by facilitating its removal in areas that are particularly hairy (rinsing away instead of pulling off).

The dissolution tests, carried out in distilled water with the apparatus described by USP 23 and with paddle rate of 100 r.p.m. at a temperature of 32 ±0.5°C, revealed that all the active principle contained in the plaster was released completely within 40 minutes from the start of the experiment. This means that the quantity of medicament that permeates and the rate at which this process takes place (bioavailability) lie exclusively in the capacity of the medicament to pass through the horny layer and to reach the epidermis and dermis.

Hence, in so far as the plaster presents characteristics of immediate release of the medicament, the formulation is used in the treatment of localized cutaneous affections that require prompt availability of the active principle associated, with permanence of the latter in the site of action . Such affections may include local inflammation and minor allergic reactions, such as insect stings, and infected cutaneous ulcerations. In all these cases, to the adhesive matrix a suitable medicament is added belonging to the classes of non-steroidal anti-inflammatory agents, such as ibuprofen, naproxen, piroxicam, ketoprofen, and acetyl salicylic

acid; steroidal anti-inflammatory agents for topical use, chosen from among dexamethasone, hydrocortisone, flucinolone, clobetasol, methylprednisolone, and betamethasone; antihistaminic agents, such as promethazine, terfenadine, cetirizine, ketotifen, astemizole, loratadine, azelastine, levocabastine, fenbenzamine, tripelennamine, chloropyramine, methaphenilene, thenyldiamine, bromopyrilene, chloropyrilene, methafurilene, methapyrilene, and or antibiotics belonging to the classes of beta-lactams, tetracyclines, macrolides, aminoglycosides, azithromycin, clarithromycin and clyndamicin.

Finally, since the plaster may be applied also in injured areas of the skin, it may perform a protective action in regard to external traumatic agents, as well as performing the function of depot for the medicament.

The example given below has exclusively the purpose of providing an illustration without having any limiting effect.

**Example**

The percentage composition of the backing layer, which constitutes the first layer, is the following:

| | |
|---|---|
| Polymethacrylate (40% aqueous dispersion) | |
| (Eudragit NE 40 D - Rofarma S.r.l., Italy) | 94.8% |
| NaCl | 0.25% |
| $H_2O$ | 3.65% |
| Hydroxypropyl cellulose (Klucel - Aqualon, USA) | 0.3% |
| Glycerine | 1% |

In practice, 10 g of the dispersion according to the formula given above are spread out over 200 $cm^2$ of a glass plate slightly smeared with silicone oil to facilitate detachment of the film at the end of the preparation, and dried in an air-circulation oven for 1 hour at a temperature of 40°C.

The composition of the second layer, which acts as a depot for the medicament and at the same time as an adhesive, is given below according to the quantity of active principle present:

4 mg of PROMETHAZINE HYDROCHLORIDE for plaster having a surface of 4 $cm^2$

| | |
|---|---|
| Polyaminomethacrylate (Plastoid E 35 L - Rofarma S.r.l., Italy) | 70% |
| Promethazine hydrochloride | 1% |
| NaCl | 0.2% |
| Sorbitol | 0.9% |
| $H_2O$ | 27.9% |

10 mg of PROMETHAZINE HYDROCHLORIDE for plaster having a surface of 4 $cm^2$

| | |
|---|---|
| Polyaminomethacrylate (Plastoid E 35 L - Rofarma S.r.l., Italy) | 70% |
| Promethazine hydrochloride | 2.5% |
| NaCl | 0.2% |
| Sorbitol | 0.9% |
| $H_2O$ | 26.4% |

The preparation of the plaster with addition of 4 mg of active principle is as follows:

20 g of dispersion containing polyaminomethacrylate, NaCl, sorbitol, promethazine hydrochloride and water are spread out over a film containing the backing layer, having a surface of 200 $cm^2$.

The ensemble of backing layer and adhesive thus obtained is put in an air-circulation oven for 1 hour at 90°C. After cooling to room temperature, it is stripped off and adhered to a protective liner; in this way, a sheet consisting of liner, adhesive layer and backing layer is obtained, out of which round plasters are cut having a surface of 4 $cm^2$.

The preparation of the plaster with addition of 10 mg of active principle is made starting from a mixture containing 2.5% promethazine hydrochloride and following the same procedure as for the preparation of the previous plaster.

Permeation tests conducted *in vitro* using the skin of the external part of ears of pigs aged between 10 and 11 months, having a thickness of approximately 1 mm, revealed that, in the absence of electric current, passive transportation of the medicament was very low in the case of the plaster containing 4 mg of promethazine and decidedly higher in the case of the plaster containing 10 mg of

promethazine. The application of an electric current, having a density of 0.5 $mA/cm^2$, for a period of 30 minutes considerably increased the transport of promethazine hydrochloride with both plasters.

Also *in vivo* tests were conducted in order to determine the antihistaminic activity of both of the plasters containing 4 mg of promethazine and of those containing 10 mg of promethazine. Double-blind tests were carried out on 10 healthy volunteers of both sexes and aged between 25 and 30 years. A small allergic reaction, similar to that caused by the bite of a mosquito, was caused by using a 1% histamine solution. The depositing of a given quantity of the said solution (20 microlitres) on the inner part of the forearm and the subsequent puncture using a special disposable intradermic needle caused penetration of the histamine into the more superficial layers of the dermis, giving rise to the triple response referred to previously. The pictures of the weal, taken by a telecamera mounted on a stereoscopic microscope, were recorded and processed using an appropriate image-processing program, in order to obtain the dimensions of the weal at preset time intervals.

The inhibitory action of the promethazine hydrochloride on the formation of the weal, due to the application of the plaster on the lesion two minutes after the puncture, was compared with the evolution of a second weal which had not been treated pharmacologically and which had been caused in the same conditions in an area on the contralateral side to the area that had undergone pharmacological treatment. The volunteer was then asked to assess the sensation of itching according to the following scale: 5, very intense itching; 4 intense itching; 3, medium itching; 2 mild itching; 1 very light itching; 0, no itching.

These experiments revealed that the size of the weal, after reaching an area of approximately 18 $mm^2$ within 15-17 minutes, decreased rapidly to half that area owing to the application of the plaster containing 4 mg of promethazine. A similar result, albeit more effective, was obtained using the plaster containing 10 mg of promethazine. In fact, the percentage reduction of the weal proved to be of between 20% and 30% in the case of the plaster containing 4 mg of promethazine, whereas, in the case of the plaster containing 10 mg of promethazine, a reduction of between 30% and 50% was obtained within 30

minutes.

In addition, the assessment requested from each volunteer as regarded the sensation of itching during formation of the weal revealed that the treatment with the plaster, whether the one containing 4 mg or the one containing 10 mg of promethazine, was able to cause faster disappearance of the symptom after the peak value was reached, as compared with the lesion to which the placebo had been applied.

Figure 1 shows the curves of the pattern of pruritus as a function of time, both after application of the plaster containing promethazine hydrochloride (4 mg and 10 mg) and after application of a plaster without any pharmacological treatment (plaster without active principle, i.e., placebo).

The area under the curve, which represents the total amount of pruritus, was found to be 45.9 in the case of the plaster with the lower dose, 42.4 in the case of the plaster containing 10 mg, and 65.8 in the case of application of the placebo.

The same type of *in vivo* experiment was conducted massaging the skin for 1 minute after application both of the plaster containing 4 mg and of the plaster containing 10 mg of promethazine hydrochloride. The results obtained (Figure 2) revealed that the weals, after reaching an area of approximately 16 $mm^2$ in 15 minutes, decreased rapidly: the percentage reduction of the weal was found to be 35% in the case of the plaster containing 4 mg of medicament, whereas in the case of the plaster containing 10 mg, it was approximately 50%.

The assessment of the pruritus during formation of the weal revealed that treatment with the plaster, whether the one containing 4 mg of promethazine hydrochloride or the one containing 10 mg of promethazine hydrochloride, was able to cause faster disappearance of pruritus than when the skin was not massaged. The area under the pruritus values-versus-time curve was 28.8 in the case of the plaster with 4 mg of promethazine, 24.1 in the case of the plaster containing 10 mg, and 39.2 in the case of application of the placebo. The results obtained show that, after application of either type of medicated plaster, the amount of pruritus was reduced by approximately one half with respect to the case where no massaging was applied, this reduction being present also in the case of the placebo.

Finally, a third type of test was carried out by subjecting each volunteer to 1 minute of ionophoresis (current density, 0.25 $mA/cm^2$), both after application of the plaster containing promethazine hydrochloride (4 mg or 10 mg) and after application of a plaster without any pharmacological treatment.

The results showed that the weals, after reaching an area of approximately 16 $mm^2$ in 15 minutes, rapidly decreased by one half as a result of the application of the plaster with ionophoretic treatment.

In addition, the assessment requested from each volunteer of the pruritus experienced during formation of the weal revealed that treatment with the plaster and ionophoresis was able to cause a faster disappearance of pruritus as compared to the results obtained without application of ionophoresis (Figure 3). The area under the curve of the pruritus values experienced during formation of the weal was 17.8 in the case of the plaster with 4 mg of promethazine, 18.5 in the case of the plaster containing 10 mg, and 26.4 in the case of application of the placebo. The results also showed that the application of electric current (ionophoresis) is able to reduce pruritus considerably even when the placebo alone is used.

## CLAIMS

1. Dermal plaster having high mechanical strength, flexibility, transparency and electric conductivity, comprising:

a) a backing layer containing:

- a polymer insoluble in water,
- a thickening agent,
- a humectant;

b) an adhesive layer possibly containing the active principle and:

- an adhesive polymer,
- a humectant,

characterized in that both the backing layer and the adhesive layer contain an electrolyte.

2. Dermal plaster according to Claim 1, containing an active principle selected from the group consisting of an antihistaminic agent, a non-steroidal anti-inflammatory agent, a steroidal anti-inflammatory agent for topical use, an antibiotic, or mixtures thereof.

3. Dermal plaster according to Claim 2, in which the antihistaminic agent is selected from the group consisting of from among promethazine, terfenadine, cetirizine, ketotifen, astemizol, loratadine, azelastine, levocabastine, fenbenzamine, tripelennamine, chloropyramine, methaphenilene, thenyldiamine, bromopyrilene, chloropyrilene, methafurilene, methapyrilene.

4. Dermal plaster according to Claim 2, in which the non-steroidal anti-inflammatory agent selected from the group consisting of ibuprofen, naproxen, piroxicam, ketoprofen, and acetyl salicylic acid.

5. Dermal plaster according to Claim 2, in which the steroidal anti-inflammatory agent for topical use is chosen from among the group consisting of dexamethasone, hydrocortisone, flucinolone, clobetasol, methylprednisolone, and betamethasone.

6. Dermal plaster according to Claim 2, in which the antibiotic is selected from the class consisting of: antibiotics belonging to the classes of beta-lactams, tetracyclines, macrolides, aminoglycosides, azithromycin, clarithromycin, and clindamycin.

7. Dermal plaster according to any one of the Claims from 1 to 6, characterized in that the electrolyte is a halide of an alkaline or alkaline-earth metal.

8. Dermal plaster according to Claim 7, characterized in that the electrolyte is selected from the group consisting of sodium chloride, potassium chloride and magnesium chloride.

9. Dermal plaster according to any one of the Claims from 1 to 8, characterized in that the composition used to prepare the backing layer and the adhesive layer contains the electrolyte in a concentration of between 0.001% and 5% each.

10. Dermal plaster according to any one of the Claims from 1 to 9, characterized in that the composition used for the preparation of the backing layer comprises between 50% and 99% of an aqueous suspension or dispersion containing the said water-insoluble polymer, selected from the group consisting of: polyethylene, polypropylene, polyethylene, polyacrylate, polyethylene terephthalate, polypropylene terephthalate and polymethacrylate.

11. Dermal plaster according to Claim 10, characterized in that the composition used for the preparation of the backing layer contains between 80% and 99% of the said aqueous suspension or dispersion.

12. Dermal plaster according to Claim 10 or Claim 11, characterized in that the said aqueous dispersion or suspension contains 40% esters of polymethacrylic acid.

13. Dermal plaster according to any one of the Claims from 1 to 12, characterized in that the thickening agent used in the composition used for the preparation of the backing layer is selected from the group consisting of xanthan gum and cellulose or derivatives thereof, and is present in a concentration of between 0.005 % and 5 % by weight.

14. Dermal plaster according to Claim 13, characterized in that the composition of the backing layer contains hydroxypropyl cellulose as thickening agent.

15. Dermal plaster according to any one of the Claims from 1 to 14, characterized in that the humectant, which is contained both in the backing layer and in the adhesive layer of the dermal plaster, is selected from the group consisting of glycerine, sorbitol, propylene glycol, and polyethylene glycol.

16. Dermal plaster according to Claim 14, characterized in that the composition

used for the preparation of the backing layer and that used for the preparation of the adhesive layer contain the humectant at a concentration of between 0.01 % and 5 % by weight each.

17. Dermal plaster according to Claim 16, characterized in that the said substance able to maintain a certain degree of humidity in the backing layer is glycerine.

18. Dermal plaster according to any one of the Claims from 1 to 17, characterized in that the adhesive polymer present in the adhesive layer is selected from the group consisting of polyaminomethacrylate, polyisobutylene, silicone, polyvinyl alcohol, arabic gum, rosin, abietic acid and derivatives thereof.

19. Dermal plaster according to Claim 18, characterized in that the composition used for the adhesive layer contains from 5 % to 90 % by weight of an aqueous dispersion containing the adhesive polymer.

20. Dermal plaster according to Claim 19, characterized in that the said aqueous dispersion contains from 20 % to 40 % by weight of polyaminomethacrylate.

21. Dermal plaster according to Claim 15, characterized in that the humectant in the composition used for the preparation of the adhesive layer is sorbitol.

22. Dermal plaster according to any one of the previous Claims from 1 to 21, used for the treatment of localized skin affections.

23. Dermal plaster according to Claim 22, characterized in that the said localized skin affections are insect stings and infected local ulcerations.

24. Dermal plaster according to any one of the Claims from 1 to 23, characterized in that an electric current or laser radiation is applied to it.

25. Dermal plaster according to Claim 24, characterized in that, after the plaster has been applied on the skin, a direct electric current having a density of between 0.01 and 0.8 $mA/cm^2$ is applied to it.

26. Dermal plaster according to any one of the Claims from 1 to 23, characterized in that, after the plaster has been applied on the skin, mild manual massaging is applied.27. Dermal plaster according to any one of the claims 1 and 7-23, which does not contain the active principle, characterized in that, after the plaster has been applied on the skin, an electric current is applied to it.

28. Dermal plaster according to Claim 27, characterized in that, after the plaster has been applied on the skin, a direct electric current is applied to it having a

density of between 0.01 and 0.8 $mA/cm^2$.

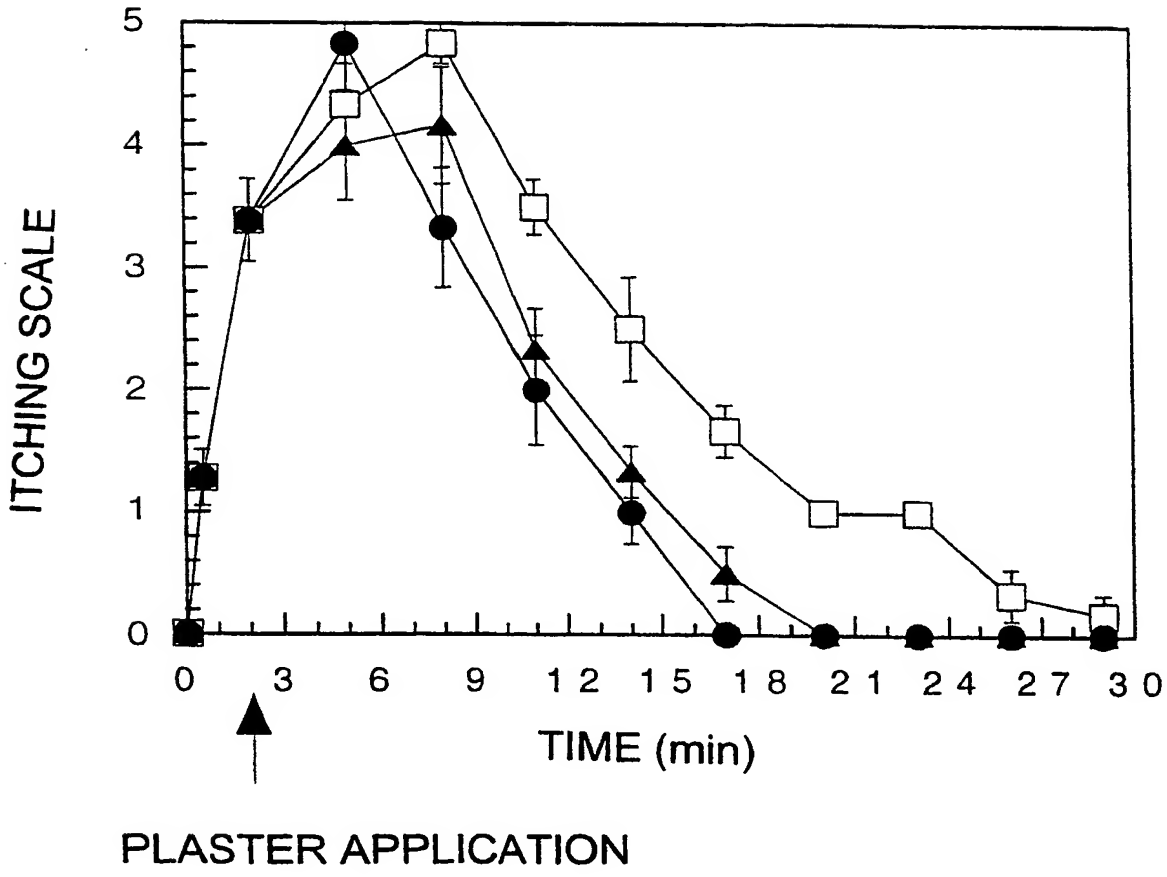


Fig. 1

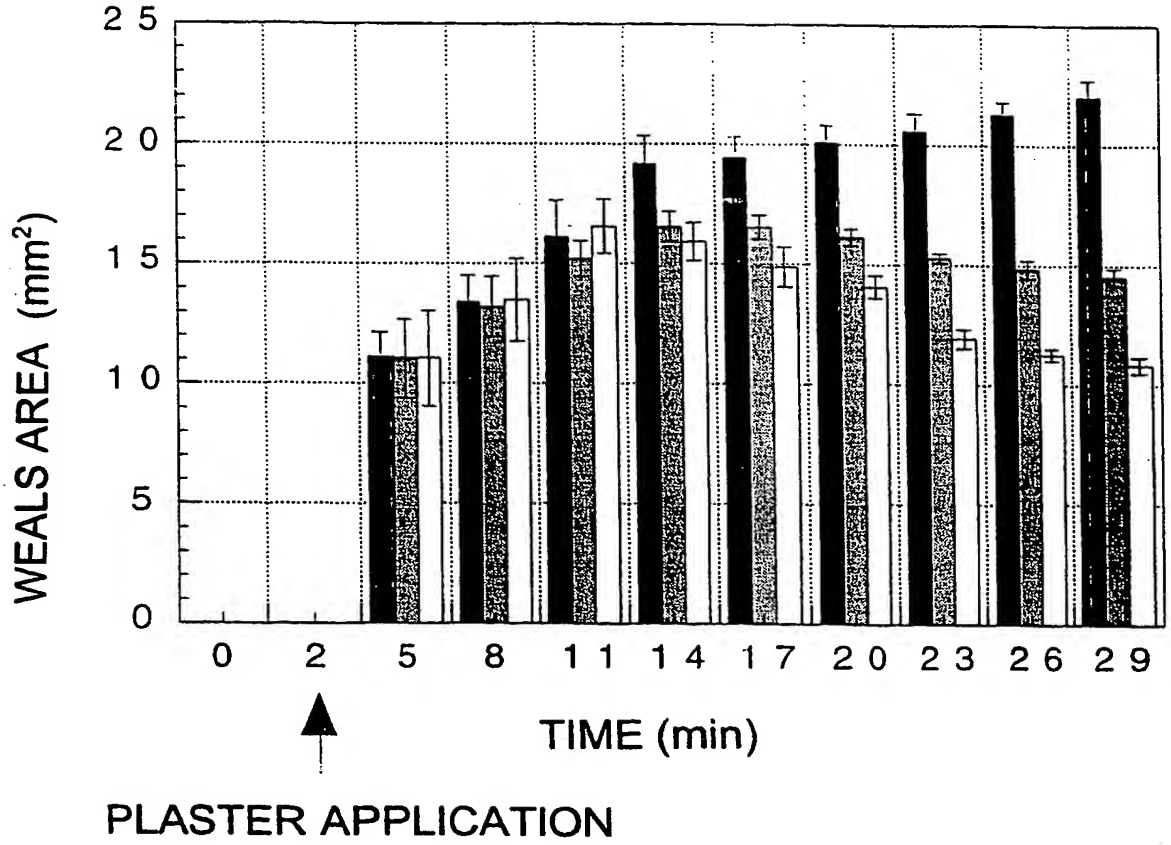


Fig. 2

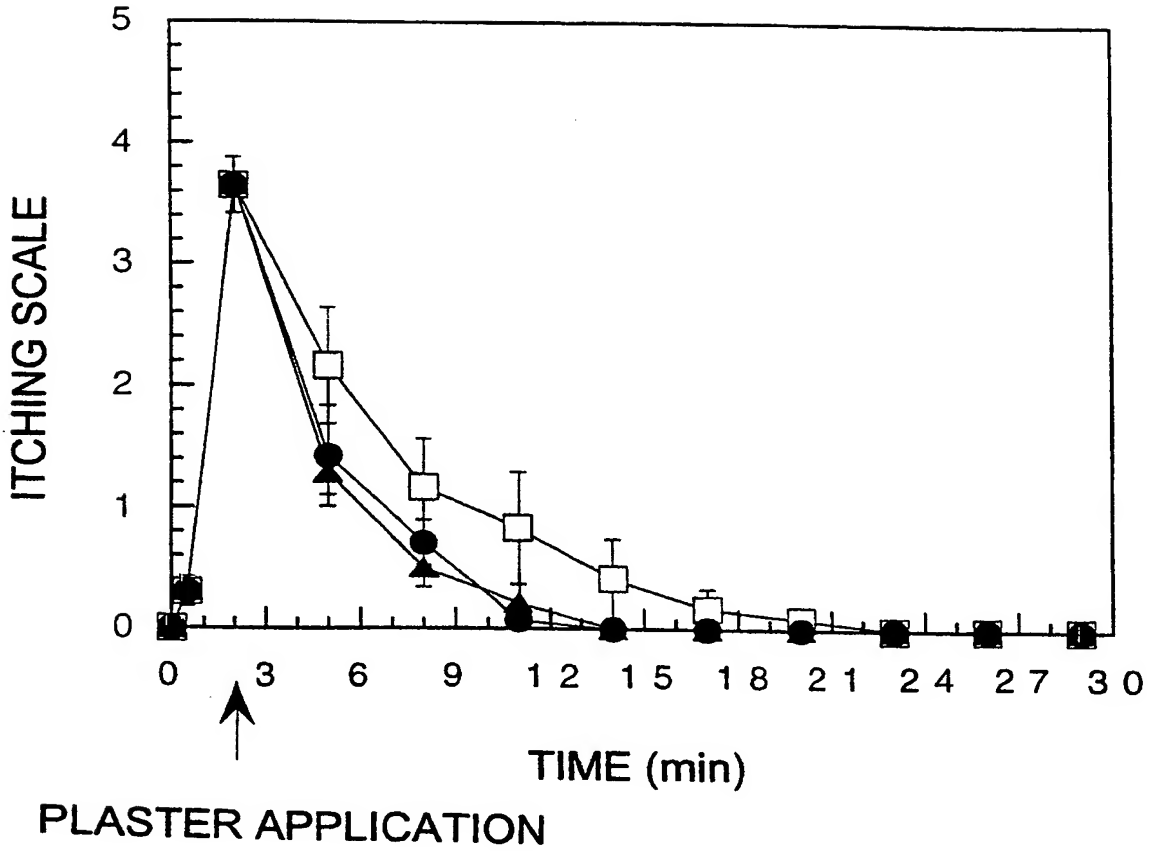


Fig. 3

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int tional Application No
PCT/EP 98/03796

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| EP 0846473 A | 10-06-1998 | WO 9706847 A | 27-02-1997 |
| | | AU 3193395 A | 12-03-1997 |
| | | JP 8010340 A | 16-01-1996 |
| EP 0269246 A | 01-06-1988 | JP 1872334 C | 26-09-1994 |
| | | JP 63102768 A | 07-05-1988 |
| | | DE 3783877 A | 11-03-1993 |
| | | KR 9513631 B | 13-11-1995 |
| | | US 4842577 A | 27-06-1989 |
| WO 9310201 A | 27-05-1993 | US 5276079 A | 04-01-1994 |
| | | AT 146212 T | 15-12-1996 |
| | | AU 657188 B | 02-03-1995 |
| | | AU 3125493 A | 15-06-1993 |
| | | CA 2116123 A | 27-05-1993 |
| | | DE 69215893 D | 23-01-1997 |
| | | DE 69215893 T | 03-04-1997 |
| | | DK 612342 T | 16-06-1997 |
| | | EP 0612342 A | 31-08-1994 |
| | | JP 7501101 T | 02-02-1995 |
| | | US 5438988 A | 08-08-1995 |
| | | US 5409966 A | 25-04-1995 |
| | | US 5389376 A | 14-02-1995 |

# INTERNATIONAL SEARCH REPORT

Int ational Application No
PCT/EP 98/03796

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61L15/18 A61L15/44 A61K9/70 A61K9/00 A61N1/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| P,X | EP 0 846 473 A (HISAMITSU PHARMACEUTICAL CO) 10 June 1998<br>see abstract<br>see column 1, line 40 - line 50<br>see column 2, line 10 - line 15<br>see column 2, line 45 - column 3, line 4<br>see column 3, line 57 - line 58<br>see column 4, line 5 - line 6<br>see column 5, line 44 - column 6, line 34<br>see column 7, line 15 - line 35<br>-& WO 97 06847 A<br>--- | 1-22,24 |
| X | EP 0 269 246 A (YAMANOUCHI PHARMA CO LTD) 1 June 1988<br>see abstract<br>see page 2, line 40 - line 54<br>---<br>-/-- | 1-22,24 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 3 December 1998 | 14/12/1998 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Gundlach, B |

2

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

Int itional Application No
PCT/EP 98/03796

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 93 10201 A (MINNESOTA MINING & MFG)<br>27 May 1993<br>cited in the application | 1,2,6 |
| A | see page 8, line 31 - line 37<br><br>see page 9, line 29 - line 43<br>see page 10, line 18 - line 43 | 3-5,<br>7-20,<br>22-28 |
| A | PATENT ABSTRACTS OF JAPAN<br>vol. 009, no. 200 (C-298), 16 August 1985<br>& JP 60 069016 A (NITTO DENKI KOGYO KK),<br>19 April 1985<br>cited in the application<br>see abstract | 1,2,5,<br>22,23 |





Form PCT/ISA/210 (continuation of second sheet) (July 1992)